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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/844,257	04/27/2001	Karin Kellner	CIBT-P01-099	8923

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EXAMINER	
BRANNOCK, MICHAEL T	
ART UNIT	**PAPER NUMBER**
1646	12

DATE MAILED: 11/03/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/844,257	KELLNER ET AL.	
	Examiner	Art Unit	
	Michael Brannock	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *29 May 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *1-15* is/are pending in the application.

4a) Of the above claim(s) *9-15* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1-8* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *19 September 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *5 and 6* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Status of Application: Claims and Amendments

Claims 10-15 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 9 and 10.

The traversal is on the grounds that a search of Groups I and II would not be a serious burden on the examiner. This is not found persuasive for the following reasons:

Under MPEP § 803, there are two criteria for a proper requirement for restriction between patentably distinct inventions:

(A) The inventions must be independent (see MPEP § 8702.01, 806.04, 808.01) or distinct as claimed (see MPEP § 806.05- §806.05(I)): and

(B) There must be a serious burden on the examiner if restriction is required (see MPEP § 803.02, § 806.04(a)- 806.04(I), § 808.01(a), and § 808.02).

Consistent with current patent practice, a serious search burden may be established by (A) separate classification thereof: (B) a separate status in the art when they are classifiable together: (C) a different field of search. These criteria were met in the above restriction. Further, a search is directed not only to art which would be anticipatory, but also to art that would render the invention obvious. In the instant case, the intermediate product of group II is distinct from that of Group I because it is useful to make other than the final product, i.e. the tissue culture system of Group II can be used other than to make a prosthesis, e.g. as a tool to study the development of cartilage and musculature. Further, Applicant is correct that the claims of Group I claim a method and not a product, however, for the analysis of the restriction requirement, it is obvious that the claims require that a product be made. Although a search of

the of Group I would overlap a search of Group II, the two searches would not be coextensive Thus, Groups I and II require divergent searches, and to search both inventions would be burdensome. Additionally, Applicant's election of the species comprising di-palmitoyl sonic hedgehog and collagen is acknowledged, however no arguments were presented as to the merits of the species election requirement. Therefore, the restriction is maintained and made final.

Priority

Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119e as follows:

An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification of in an application data sheet (37 CFR 1.78(a)(2) and (a)(5)). The specific reference to any prior nonprovisional application must include the relationship (i.e., continuation, divisional, or continuation-in-part) between the applications except when the reference is to a prior application of a CPA assigned the same application number.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-8 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, for the following reasons:

Claim 1 recites the phrase "hedgehog therapeutic". The specification defines "hedgehog therapeutic" as hedgehog protein or peptidomimetics that can modulate the proliferation or differentiation state of chondrocytes directly or indirectly. The specification then provides some examples of "hedgehog therapeutics", pgs 6-7. Thus, because a "hedgehog therapeutic" can affect hedgehog signaling either directly or indirectly, the term appears to encompass any and all compounds that alter the activity of the many different hedgehog proteins as well as the activities of their receptors e.g. patched (ptc-1 and ptc-2) and any other downstream effects, e.g. Smoothen, Gli1-3, etc. However, it is well appreciated that the activities of these pathways are extremely complex and as yet controversial and incompletely identified (see Stull and Iacovitti, Experimental Neurobiology 169(1)36-43, 2001, especially page 40), therefore the phrase "hedgehog therapeutic" renders the claims indefinite because those skilled in the art would have to identify the activities of the known patched and hedgehog polypeptides in order to determine whether a compound alters these activities, as they relate to any effect particular effect on any particular aspect of chondrocyte proliferation or differentiation.

Further the recitation of the term " hedgehog polypeptide" without reference to a particular amino acid or nucleic acid sequence renders the claims indefinite because the specification has not put forth that material or functional element that is indicative of a "hedgehog polypeptide" and nor is such a definition known in the prior art which clearly sets forth which polypeptides are hedgehog polypeptides and which are not. Therefore the metes and bounds of the claims cannot be determined.

Additionally, claims 5-7 recite the term "di-palmitoyl" or "dipalmitoyl hedgehog protein". These terms do not appear to be recognized in the art. The examiner does not

understand the definition of these terms as they are defined at page 11 of the specification. Thus, an artisan could not be reasonably certain whether or not he or she was practicing the claimed invention because of the presence of these terms.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-4, 6, 11 and 12 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of making a cartilaginous prosthesis comprising contacting the construct with a naturally occurring hedgehog polypeptide, or the N-terminal autoproteolytic fragment thereof, does not reasonably provide enablement for such methods comprising the administration of polypeptides other than a naturally hedgehog polypeptide or for the genus of "peptidyl fragments" thereof (e.g. page 7, L 20). The specification does not enable a person skilled in the art to which it pertains, or with which it is most nearly connected, to the invention commensurate in scope with these claims.

The specification presents the results obtained with the N-terminal autoproteolytic fragments of several naturally occurring hedgehog proteins. The claims claim methods using any polypeptide that could be termed a "hedgehog therapeutic" e.g. any artificially produced hedgehog protein or mimetic, yet the specification has not provided sufficient guidance as to which other polypeptides or mimetics, or fragments would work as claimed. The specification

has simply presented an invitation to the skilled artisan to try to find such fragments other than that corresponding to the naturally occurring N-terminal autoproteolytic fragment (e.g. claim 4). The art recognizes that it is this fragment that is required for activity and that even small deletions of it abolish activity, see Marti, S. et al., Nature 375(322-325)1995, particularly col 1 of page 323 and Figure 1a. Further, the claims encompass variants of the disclosed hedgehog polypeptides, i.e., the specification contemplates such variants as being encompassed by the term "hedgehog polypeptide" (see page 7 for example), yet the specification has not provided sufficient guidance as to how to make such variants. One of skill in the art is left to extensive experimentation wherein amino acids are randomly changed, deleted, or added to a hedgehog polypeptide, and through trial and error experimentation is left to determine when a polypeptide is obtained that could used to in a cartilaginous prosthesis. Such extensive random trial and error experimentation is considered undue.

The problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein, the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These or other regions may also be critical determinants of antigenicity. These regions can tolerate only relatively conservative substitutions or no substitutions (see Bowie et al., 1990, Science 247:1306-1310, especially

p.1306, column 2, paragraph 2. However, Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions. Although the specification outlines art-recognized procedures for producing and screening for active muteins, this is not adequate guidance as to the nature of active variants or portions that may be constructed, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. Even if an active or binding site were identified in the specification, they may not be sufficient, as the ordinary artisan would immediately recognize that an active or binding site must assume the proper three-dimensional configuration to be active, which conformation is dependent upon surrounding residues; therefore substitution of non-essential residues can often destroy activity.

Due to the large quantity of experimentation necessary to generate the almost limitless number of variants and portions required by the claims and screen same for activity, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function, and the breadth of the claims, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-4 and 8 are rejected under 35 U.S.C. 102(a) and 102(e) as being anticipated by U.S. Patent No: 5844079 to Ingham et al.

Ingham et al. disclose a method of making a cartilaginous prosthesis comprising seeding a polymeric matrix of articular chondrocytes and contacting the seeded construct with a naturally occurring hedgehog polypeptide, see col 50, particularly lines 40-68. Wherein the polymer matrix is polyglycolid acid (see col 50, L55); and a wherein the naturally occurring hedgehog polypeptide is hydrophobically modified, e.g. with a lipid moiety (see col 28, line 29).

Conclusion

No claims are allowable.

Please note the new official fax number below:

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Brannock, Ph.D., whose telephone number is (703) 306-5876. The examiner can normally be reached on Mondays through Thursdays from 8:00 a.m. to 5:30 p.m. The examiner can also normally be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, Ph.D., can be reached at (703) 308-6564.

Official papers filed by fax should be directed to (703) 872-9306. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

MB

October 31, 2003

GARY KUNZ
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600